Amendments to the Claims:

1. (Original) A method for identifying a ligand binding to an inactive conformation of a target protein kinase, comprising

(a) contacting the inactive conformation of said target protein kinase, which contains or is modified to contain a reactive group at or near a binding site of interest, with one or more ligand candidates capable of covalently bonding to said reactive group thereby forming a kinase-ligand conjugate; and

(b) detecting the formation of said kinase-ligand conjugate and identifying the ligand present in said kinase-ligand conjugate.

2. (Original) The method of claim 1 wherein said reactive group is capable of forming a disulfide bond with said ligand candidate.

3. (Original) The method of claim 2 wherein said reactive group is a thiol group, masked thiol group, or activated thiol group, which forms a disulfide bond with a thiol functionality present on said ligand candidate.

4. (Original) The method of claim 3 wherein said thiol functionality is present as part of a flexible linking group.

5. (Original) The method of claim 4 wherein said flexible linking group is of the form $-(CH_2)_n$-S-S-$CH_2CH_2NH_2$, wherein n is 1 to 5.

6. (Original) The method of claim 1 wherein said target protein kinase is contacted with a plurality of said ligand candidates.

7. (Original) The method of claim 1 wherein said ligand is less than 1500 daltons in size.

8. (Original) The method of claim 1 wherein said ligand is less than 1000 daltons in size.

9. (Original) The method of claim 1 wherein said ligand is less than 750 daltons in size.

10. (Original) The method of claim 1 wherein said ligand is less than 500 daltons in size.

11. (Original) The method of claim 1 wherein said target protein kinase is locked in inactive conformation by alteration of at least one amino acid residue at an inactivation site.

12. (Original) The method of claim 11 wherein said alteration is an amino acid substitution.

13. (Original) The method of claim 12 wherein an alanine residue is substituted for a wild-type amino acid residue at said inactivation site.

14. (Original) The method of claim 11 wherein said inactivation site is selected from the group consisting of the invariant aspartic acid residue in the catalytic loop, the arginine residue in the catalytic loop, the invariant aspartic acid residue in the DFG motif, and the invariant lysine residue in motif II of said target protein kinase.

15. (Original) The method of claim 1 wherein said target protein kinase contains said reactive group without further modification.

16. (Original) The method of claim 15 wherein said reactive group is a cysteine residue.

17. (Original) The method of claim 1 wherein said target protein kinase is modified to contain said reactive group.

18. (Original) The method of claim 17 wherein said reactive group is a cysteine residue.

19. (Original) The method of claim 2 wherein said target protein kinase and said ligand candidate are contacted in the presence of a reducing agent.

20. (Original) The method of claim 19 wherein said reducing agent is 2-mercaptoethanol or cysteamine.

21. (Original) The method of claim 1 wherein the formation of said kinase-ligand conjugate is detected by mass spectrometry.

22. (Original) The method of claim 21 wherein the kinase-ligand conjugate is subjected directly to mass spectrometry analysis.

23. (Original) The method of claim 22 wherein the kinase-ligand conjugate is fragmented prior to mass spectrometry analysis.

24. (Original) The method of claim 22 or claim 23 wherein the mass spectrometry analysis also identified the ligand in said conjugate.

25. (Original) The method of claim 1 wherein the kinase-ligand conjugate is detected using NMR.

26. (Original) The method of claim 25 wherein NMR also identifies the ligand in said conjugate.

27. (Original) The method of claim 1 wherein the kinase-ligand conjugate is detected using X-ray crystallography.

28. (Original) The method of claim 27 wherein X-ray crystallography also identifies the ligand in said conjugate.

29. (Original) The method of claim 1 wherein the kinase-ligand conjugate is detected using capillary electrophoresis.

30. (Original) The method of claim 1 wherein the kinase-ligand conjugate is detected using high performance liquid chromatography.

31. (Original) The method of claim 1 comprising identifying at least two ligands binding to non-overlapping binding sites of interest of the inactive conformation of said protein kinase.

32. (Original) The method of claim 31 further comprising the step of synthesizing a molecule comprising said ligands.

33. (Original) A method for identifying a ligand that binds to the inactive conformation of a target protein kinase, comprising

(a) obtaining the inactive conformation of said target protein kinase comprising an -SH group, masked -SH group, or activated -SH group;

(b) combining said inactive conformation of said target protein kinase with one or more ligand candidates wherein said ligand candidates each comprises a disulfide bond;

(c) forming a kinase-ligand conjugate wherein at least one ligand candidate binds to the inactive conformation of the target protein kinase under disulfide exchange conditions, and

(d) detecting the formation of said kinase-ligand conjugate and identifying the ligand present in said conjugate.

34. (Original) The method of claim 33 wherein said target protein kinase is locked in an inactive conformation by an amino acid substitution at one or more sites selected from the group consisting of the invariant aspartic acid residue in the catalytic loop, the arginine residue in the catalytic loop, the invariant aspartic acid residue in the DFG motif, and the invariant lysine residue in motif II of said target protein kinase.

35. (Original) The method of claim 33 wherein said -SH group, masked -SH group, or activated -SH group is provided by a cysteine residue.

36. (Original) The method of claim 35 wherein said target protein kinase is modified to contain a cysteine residue.

37. (Original) The method of claim 33 wherein said target protein kinase and said ligand candidate are contacted in the presence of a reducing agent.

38. (Original) The method of claim 37 wherein said reducing agent is 2-mercaptoethanol or cysteamine.

39 (Original) The method of claim 33 wherein said ligand is a non-peptide small organic molecule, less than 1500 daltons in size.

40. (Original) The method of claim 33 wherein said ligand is a non-peptide small organic molecule, less than 1000 daltons in size.

41. (Original) The method of claim 33 wherein said ligand is a non-peptide small organic molecule, less than 750 daltons in size.

42. (Original) The method of claim 33 wherein said ligand is a non-peptide small organic molecule, less than 500 daltons in size.

43. (Original) The method of claim 33 wherein the formation of said kinase-ligand conjugate is detected by mass spectrometry.

44. (Original) The method of claim 33 wherein the kinase-ligand conjugate is subjected directly to mass spectrometry analysis.

45. (Original) The method of claim 33 wherein the kinase-ligand conjugate is fragmented prior to mass spectrometry analysis.

46. (Original) The method of claim 44 or claim 45 wherein the mass spectrometry analysis also identified the ligand in said conjugate.

47. (Withdrawn) A method for identifying ligands binding to an inactive conformation of a target protein kinase, comprising

(a) contacting the inactive conformation of said protein kinase having a first and a second binding site of interest and containing or modified to contain a nucleophile at or near the first site of interest with a plurality of ligand candidates, said candidates having a functional group reactive with the nucleophile, under conditions such that a reversible covalent bond is formed between the nucleophile and a candidate that has affinity for the first site of interest, to form a kinase-first ligand complex;

(b) identifying the first ligand from the complex of (a);

(c) designing a derivative of the first ligand identified in (b) to provide a small molecule extender (SME) having a first functional group reactive with the nucleophile on the kinase and a second functional group reactive with a second ligand having affinity for the binding second site of interest;

(d) contacting the SME with the kinase to form a kinase-SME complex, and

(e) contacting the kinase-SME complex with a plurality of second ligand candidates, said candidates having a functional group reactive with the SME in said kinase-SME complex,

wherein a candidate that has affinity for said second binding site of interest on said kinase forms a reversible covalent bond with said kinase-SME complex, whereby a second ligand is identified.

48. (Withdrawn) The method of claim 47 wherein said nucleophile is selected from the group consisting of -SH, -OH, $-NH_2$ and -COOH groups.

49. (Withdrawn) The method of claim 48 wherein said nucleophile is provided by a side chain of an amino acid residue selected from the group consisting of cysteine, serine, threonine, lysine, asparagine, and glutamine.

50. (Withdrawn) The method of claim 49 wherein said nucleophile is an -SH group provided by the side chain of a cysteine residue.

51. (Withdrawn) The method of claim 50 wherein said kinase contains said cysteine residue without further modification.

52. (Withdrawn) The method of claim 50 wherein said kinase is modified to contain said cysteine residue.

53. (Withdrawn) The method of claim 50 wherein said SME comprises a group capable of undergoing SN2-like attack or forming a Michael-type adduct with the -SH group of said cysteine residue.

54. (Withdrawn) The method of claim 53 wherein said group is selected from the group consisting of α-halo acids, fluorophoph(on)ates, epoxides, aziridines, thiiranes, halo-methyl ketones, and halo-methyl amides.

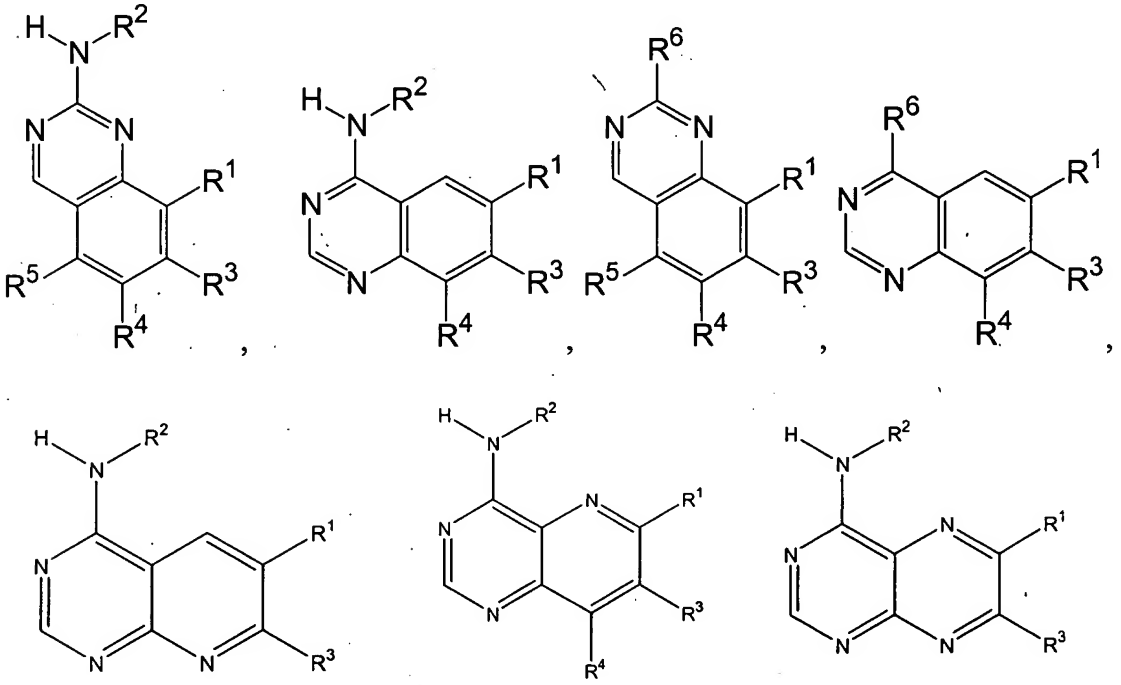
55. (Withdrawn) The method of claim 50 wherein said second functional group is an -SH group.

56. (Withdrawn) The method of claim 47 wherein wherein said ligand candidates are members of a small molecule library.

57. (Withdrawn) The method of claim 56 wherein each member of said library differs in molecular weight from each other member of said library.

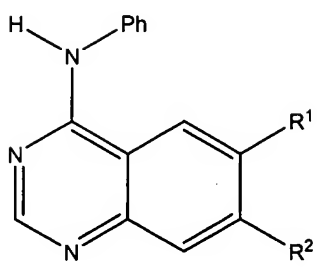
58. (Withdrawn) The method of claim 57 wherein said library contains 1 to 100 members.

59. (Withdrawn) The method of claim 47 wherein said small molecule extender is selected from the group consisting of



where R^1, R^2, R^3, R^4, R^5, and R^6 are each independently selected from the group consisting of hydrogen, C_1-C_5 alkyl, C_1-C_5 alkylamine, and aryl provided that at least one R group on the SME is a Michael acceptor or -(C=O)CH_2X where X is a halogen and another R group is selected from -$(CH_2)_n$-SR'; –C(=O)-$(CH_2)_n$-SR'; -O-$(CH_2)_n$-SR'; -$(CH_2)_n$-SR'; and a thiol protecting group, wherein R' is hydrogen or a sulfide and n is 1 to 5.

60. (Withdrawn) The method of claim 47 wherein said small molecule extender is



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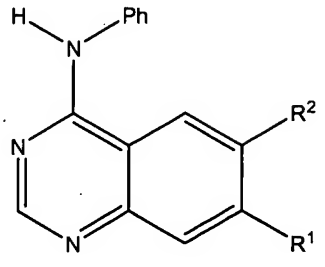
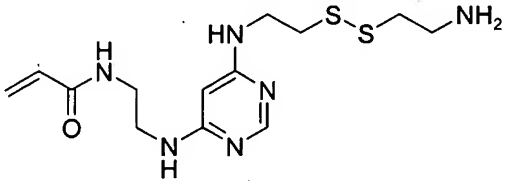
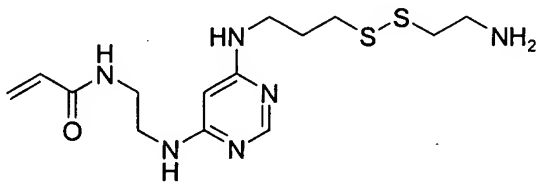
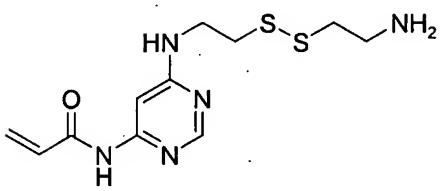


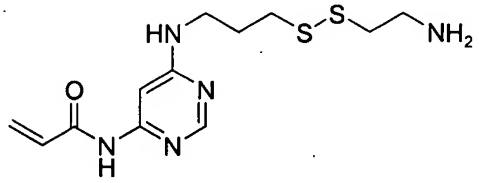
where R^1 is -NHC(=O)CH_2Cl, -NHC(=O)CH=CH_2 or -NHC(=O)CCH and R^2 is -$(CH_2)_m$SS$CH_2CH_2NH_2$ where m is 1-3.

61. (Withdrawn) The method of claim 47 wherein said small molecule extender is selected from the group consisting of









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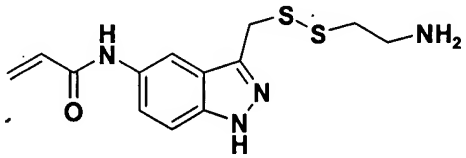

62. (Withdrawn) A method for identifying ligands binding to an inactive conformation of a target protein kinase, comprising

(a) obtaining the inactive conformation of the target protein kinase comprising an -SH group, masked -SH group, or activated -SH group;

(b) combining in a mixture the inactive conformation of the target protein kinase with a plurality of ligand candidates that are each capable of forming a disulfide bond with the -SH group, masked -SH group, or activated -SH group thereby forming at least one kinase-ligand conjugate;

(c) analyzing the mixture by mass spectrometry; and

(d) detecting the most abundant kinase-ligand conjugate that is formed and identifying the ligand thereon.

63. (Withdrawn) A method for identifying ligands binding to an inactive conformation of a target protein kinase, comprising

(a) screening a library of ligand candidates with a kinase-ligand conjugate formed by the covalent bonding of the inactive conformation of a kinase comprising a first reactive functionality with a compound that comprises (1) a second reactive functionality and (2) a chemically reactive group, wherein the second reactive functionality of the compound reacts with the first reactive functionality of the inactive conformation of said target protein kinase to form a first covalent bond such that the kinase-ligand conjugate contains a free chemically reactive group, under conditions wherein at least one member of the library forms a second covalent bond with the kinase-ligand conjugate; and

(b) identifying a further ligand that binds covalently to the chemically reactive group of the kinase-ligand conjugate.